

Issues Concerning Clinical Research Using Human Pathologic Bioresources in the Biobank Era

Research Article

Hikari Inoue, Tatsuaki Tsuruyama*

Center for Anatomical, Pathological, and Forensic Medical Research, Graduate School of Medicine, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto, Japan.

Abstract

Biobanks storing human pathologic resources have recently emerged as critical research platforms throughout the world for the discovery of biomarkers. Pathologists have not yet established policy consensus, regulations, or informed consent (IC) guidelines for the clinical use of archival pathologic resources. Obtaining broad consent from donors for biobanks in Japan is based on the expression of passive consent to use the remaining resources after pathologic diagnosis. However, genetic and proteomic studies using pathologic formaldehyde-fixed paraffin-embedded blocks (FFPE) have been developed recently and IC for the use of FFPE has become critical. In the current paper, we reviewed the Japanese guidelines for the use of human resources and discuss medical ethics criteria pertaining to IC for the use of FFPE and other formats when IC is not possible because of difficulties in contacting relatives of deceased donors. We propose the use of archival FFPE could be possible after providing official notification of its general use for clinical studies through a webpage or other information technology platform. Furthermore, we also suggest that access to samples over a sufficient term, i.e., greater than several years, is necessary. In conclusion, it is important to establish a common consent form for these institutions.

Keywords: Human Bioresource; Regenerative Medicine; Ethical Guideline.

Abbreviation: MEXT: the Japanese Ministry of Education, Culture, Sports, Science and Technology; MHLW: the Japanese Ministry of Health, Labor and Welfare.

*Corresponding Author:

Tatsuaki Tsuruyama,
Department of Diagnostic Pathology, Kyoto University Graduate School of Medicine 1 Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan.
Tel: +81-75-753-4427
Fax: +81-75-761-4493
E-mail: tsuruyam@kuhp.kyoto-u.ac.jp

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Introduction

Biobanks of archival samples, including pathologic and forensic medical tissues, are needed to analyze the genetic and environmental factors that contribute to human disease. Unlike experimental studies using animal resources, human resources are not precisely controllable during sampling, and human genetics requires mega-scale samples because of genetic polymorphisms. In addition, for personalized medicine, the repeated and long-term use of samples are inevitable, and the frequent follow-up of the

donors or participants concerning their health condition, occupation, and lifestyle (including eating habits) for epigenetic analysis would be inconvenient [1-6].

In Japan, the Tohoku Medical Megabank Organization (<http://www.megabank.tohoku.ac.jp/>) and the BioBank Japan Project of Tokyo University (src.riken.jp/english/project/person/) on the implementation of personalized medicine are government-supported large-scale biobanks, and six national medical institutes have been urged to collect millions of specimens for statistical analysis of genetic-based studies. The growth of this collection will be accelerated by the Japan Agency for Medical Research and Development (AMED), which was established in 2015 April. In the present study, we review traditional informed consent (IC) formats in the context of Japanese regulation of human research. In actuality, the approach of specified consent presents a substantial challenge. Preceding the discussion of IC, we describe the main research regulations concerning the use of human biospecimens and clarify their uniqueness in a global context.

History of Japanese Ethical Guidelines for Use of Human Resources

Japanese clinical research programs are reviewed by Institutional Review Boards (IRBs) (<http://www.mhlw.go.jp/english/>), installed according to guidelines of the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT), the Japanese Ministry of Health, Labor and Welfare (MHLW), and the Japanese Ministry of Economy, Trade and Industry (METI) (http://www.lifescience.mext.go.jp/files/pdf/n1500_01.pdf).

Japanese guidelines for medical research are classified into four types. Professional medical or academic groups have developed the first type. The second type results from the council or committee deliberations of government agencies and is subsequently announced by the relevant ministries to agencies. The third emanates from government agencies in the form of a notification. The fourth is a guide according to legislation. Except for the last type, there is no concrete law enforcing the guidelines. Good Clinical Practice (GCP) for Trials on Drugs [Notification] was issued by the Director of the Pharmaceutical Affairs Bureau, and subsequently by the Ministry of Health and Welfare [old GCP] in 1989. Regulation of research on human subjects began in the 1980s. Particularly, in 1990, the world's first gene therapy was conducted in the US and the need for gene therapy legislation in Japan was recognized. At that time, recombinant DNA technology had advanced and the clinical use of innovative gene therapies was expected to become widespread. For this reason, Guidelines Concerning Gene Therapy Clinical Research in Universities and Other Research Institutions [then the Ministry of Education, Science and Culture Notification No.79, 1994] and Guidelines for Gene Therapy Clinical Research were established in 1994. Based on these guidelines, the first gene therapy was performed in Japan in 1995 [7].

In 2000, the Japanese government planned the "Millennium Project", which aspired to create technical innovations that would produce new industries to solve many of the problems faced by humans [8]. This included research into the prevention of diseases by gene analysis and drug discovery. Because the prediction of familial disease was possible by genetic analysis, a novel ethical problem arose that had not been previously addressed. Regretfully, in the 1990s, several gene analysis studies were conducted without IC. In the wake of these incidents, the Prime Minister's Office announced Fundamental Principles of Research on the Human Genome. Additionally, Guidelines for Bioethical Problems Associated with Genetic Analysis Research (the so-called "Millennium Guidelines") were formulated by the then Ministry of Health and Welfare. In the same year, Bioethics Committee, Council for Science and Technology Japan presented the basic principles: IC on the basis of free-will, the right not to know, the right to know, the prohibition of discrimination by genetic analysis, prior review of research programs by ethical review committees, and return of research results to society. These principles became the basis of Ethical Guidelines for Human Genome/Gene Analysis Research. However, by the end of the 1990s, the government had still not regulated epidemiological studies using human bioresources because of the minimal invasiveness during sampling. However, guidelines were created for these studies in the 2000s. Thus, basic ethical guidelines have been developed corresponding to research categories (clinical medical research, epidemiologic research, genome research and other studies) according to the degree of risk to humans during sampling and to the sensitivity of genome data information. This categorization remains a feature of Japanese guidelines. Guidelines included obligations of researchers and obligations of research institutions, such as the installation of IRBs.

Ethical Guidelines for Human Genome/Gene Analysis Research

These guidelines were introduced in 2001 as guidelines for general human genome and genetic analysis research (http://www.lifescience.mext.go.jp/files/pdf/n796_00.pdf, 2008). Compliance with the guidelines is a condition for research project assistance,

such as funding support from the relevant ministries and agencies. The guidelines are mainly concerned with personal information protection, ethical board review procedures, anonymity procedures, and adequate procedures for obtaining IC, or limits to the donation of bioresources to third parties. Because it is possible to extract personal information from human samples by genome analysis, the guidelines focus on the protection of the most sensitive of the genomic information.

Ethical Guidelines for Epidemiological Research

In 2002, these guidelines were formulated according to the conclusions of the Joint Committee of MEXT and MHLW (http://www.lifescience.mext.go.jp/files/pdf/n796_01.pdf). The guidelines were developed for application to large cohort epidemiological studies, in which invasive samples are not collected from subjects. Compliance with the guidelines is a necessary condition for funding support. Additionally, compliance with the guidelines is required for other non-ministry-funded research undertaken. The guidelines define the responsibilities of the president of the research institute, the obligations of researchers, and the establishment of an IRB. The guidelines were amended several times and were most recently reviewed and amended by the relevant ministries in December 2013.

Ethical Guidelines for Clinical Studies

These guidelines were formulated in 2003 to be applied to all parties who engage in clinical research [9]. At this time, the progress of analytical technology enabled clinical research to rapidly expand. To control this situation, the guidelines encompassed the respect, dignity and human rights of individuals. In March 2014, the Science Council of Japan provided a recommendation regarding the necessity for researchers to obey the regulations. In Japan, the government made a unique definition of clinical trial studies whose purpose is to obtain new drug approval; this is distinguished from general clinical research, which is independent of the drug approval. This distinction is internationally unique. Up to this time, while trials had been regulated by quasi-legal Good Clinical Practices rules, laws underlying the regulation do not exist for independent clinical study. Compliance with the guidelines is a condition for support from the ministries, and those who violate the guidelines are subject to penalties. At the same time, compliance with the guidelines was announced for all the research institutions in Japan, with corrective measures against any potential violator announced. The Personal Information Protection Law was also endorsed in the same year and other guidelines have been amended to match this law. From the view point of guarantees of freedom to research, academic research is not the subject of Act on the Protection of Personal Information Held by Administrative Organs or the Independent Administrative Institutions Act on the Protection of Personal Information (<http://www.cas.go.jp/jp/seisaku/hourei/data/APPIHAO.pdf>); however, academic institutions are obligated to be compliant with these acts in the handling of personal information.

Integration into Ethical Guidelines for Human Subjects Research

Under the current Japanese regulations, ensuring research quality, including the prevention of research misconduct, is regarded as highly important along with the protection of subjects. The *epidemiological guidelines* and the *clinical research guidelines* underwent

revision, and were concurrently integrated into Ethical Guidelines for Human Subjects Research (2014). The revision includes provisions relating to monitoring and auditing, the conservation of research materials, and provisions relating to conflict of interest.

As mentioned above, the majority of research using human bioresources has been conducted according to guidelines without a legal basis, whereas research that includes handling embryos or the violation of human dignity has been regulated by law. Furthermore, establishment of human ES cells resulting in the loss of fertilized eggs is strictly regulated by a Ministry process. Thus, three stages of control have been implemented in Japan.

Discussion

To date, the Japanese Society of Pathology has been formulating guidelines for the sampling and storage of bioresources and management of FFPE for research use. As mentioned, the absence of a general guideline regulating storage and availability of bioresources has been an institutional barrier against the conduct of clinical research using pathologic specimens in Japan. Individual research institutes autonomously conduct clinical research by IC, dispose of sample waste, and take measures against infectious diseases with reference to Notification No. 1314 of the Pharmaceutical and Food Safety Bureau (2012), according to approval of their IRB (<http://www.jpma.or.jp/english/parj/pdf/2012.pdf>). Thus, although IRBs are expected to provide advice, they have not been sufficiently qualified by an enactment, such as the National Research Act in the US, since before 2004. For this reason, researchers assume the responsibility for planning their project while referring to Ministry guidelines, but clauses are complicated and often difficult to understand in Japan.

Many FFPEs are stored as archival samples in individual institutional repositories for long periods of time; however, the availability has been limited to analytical use.

First, the use of FFPE specimens has been greatly changed by the development of analytical methodologies, such as extraction of DNA, RNA, and protein. We have previously reported on the proteomic usability of cardiac [10] and colonic FFPE specimens [11, 12]. On the other hand, there are many kits for extracting DNA or RNA that produce RNA integrity numbers greater than 8.0. (www.qiagen.com). The notable improvement of extraction kits is a significant development that may trigger a serious issue in using FFPE specimens, because of the possible use of DNA sequences to identify donors. Therefore, more attention should be paid to the use of FFPE.

Second, there is an ethical issue on the management of IC. Our institute has studied IC for the use of FFPE since 2005 (<http://www.ec.med.kyoto-u.ac.jp/>). In principle, we cannot use archival FFPE from deceased donors if the acquisition of IC is strictly required for research use. To solve the issue of archival FFPE use in research, we are required to make an effort to communicate with the donor's relatives [13]. In regards to the difficulties in communication, it was recently reported that the overwhelming majority of families who are suddenly bereaved are willing to authorize research use of tissue taken at the time of postmortem examination [14]; the majority of families authorized retention of tissue samples for research and one-sixth agreed to whole tissue dona-

tion. According to this report, we are potentially allowed to use the tissue for use of archived FFPE, if we follow adequate ethical procedures. Therefore, we are preparing a webpage through which we will make archival FFPE broadly available for research use for a specified term. This notification is one of the opt-out means and we will make archival FFPE available when their use is not definitely refused by donors and their relations during the notification term. Of course, there are extensive discussions on the nature and length of the notification period. It is likely that a one-year period is necessary for notification according to the civil laws in Japan.

Dynamic Consent is one of the recently proposed forms in response to the development of information technology (IT), which makes contacting donors easy. Owing to these technical issues, many donors are prepared to consent broadly to future research use without frequent contact with researchers. This is an interesting method, but donors do not necessarily favor continuous contact [15].

Recently, significant developments in the usability of FFPE have had bioethical repercussions, and researchers are now faced with novel bioethics issues. However, we believe that IT technology will enable progress on such issues.

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